Claims

1. A composition comprising an isolated antigen-binding fragment specific for a subset of dendritic cells (DCs) where the subset is specifically recognized by an antibody designated AC144, AD5-13A11, AD5-17F6, AD5-4B8, AD5-5E8, AD5-14H12 or AD5-8E7.

2. The composition according to claim 1, wherein the antigen-binding fragment is or is derived from AC144.

3. The composition according to claim 1, wherein the antigen-binding fragment is or is derived from AD5-1311.

4. The composition according to claim 1, wherein the antigen-binding fragment is or is derived from AD5-4B8.

5. The composition according to claim 1, wherein the antigen-binding fragment is or is derived from AD5-17F6.

6. The composition according to claim 1, wherein the antigen-binding fragment is or is derived from AD5-5E8.

7. The composition according to claim 1, wherein the antigen-binding fragment is or is derived from AD5-14H12.

8. The composition according to claim 1, wherein the antigen-binding fragment is or is derived from AD5-8E7.

9. A composition comprising an antigen-binding fragment specific for an epitope of an antigen designated BDCA-2 (SEQ ID NO:2).

10. A composition comprising an antigen-binding fragment specific for an epitope of an antigen designated BDCA-3.

11. The composition according to claim 10, wherein BDCA-3 is a 100 kD protein.

12. A substantially isolated or concentrated cell population or subpopulation specifically recognized by a composition according to any one of claims 1-11.

13. A substantially isolated or concentrated DC population or subpopulation isolated by identification of neuropilin-1 on the surface of the cells.

14. The DC population or subpopulation according to claim 13, wherein neuropilin-1 is recognized by an antigen-binding fragment that cross-reacts with antibodies specific for BDCA-4.

15. The composition according to any one of claims 1-11 wherein the antigen-binding fragment is selected from the group consisting of whole antibodies, bispecific antibodies, chimeric antibodies, Fab, F(ab')2, single chain V region fragments (scFv), fusion polypeptides, aptomers, carbohydrates and lectins.

16. The composition according to claim 15, wherein the antigen-binding fragment is of human origin.

17. The composition according to claim 16, wherein the antigen-binding fragment is encoded by a phage display library.

18. The composition according to claim 15, wherein the antigen-binding fragment consists essentially of a scFv.

19. The composition according to claim 15, wherein the fusion peptide comprises the antigen-binding fragment fused to a chemically functional moiety.

20. The composition according to claim 19, wherein the moiety is selected from the group consisting of signal peptides, agents that enhance immunologic reactivity, antigens, agents that facilitate coupling to a solid support, bioresponse modifiers, immunotoxins, toxins, detectable labels, paramagnetic labels and drugs.

21. The composition according to claim 20, wherein the agent that facilitates coupling to a solid support is selected from the group consisting of biotin and avidin.

22. The composition according to claim 20, wherein the bioresponse modifier is a cytokine or a chemokine.

23. The composition according to claim 20, wherein the cytokine/chemokine is selected from the group consisting of IL-1, IL-2, IL-4, IL-5, IL-6, IL-12, interferons, TNF-α, IL-10 and TGF-β.

24. The composition according to claim 20, wherein the toxin is selected from the group consisting of ricin, radionuclides, pokeweed antiviral protein, Pseudomonas exotoxin A, diphtheria toxin, ricin A chain, fungal ribosome inactivating proteins and phospholipase enzymes.

25. The composition according to claim 20, wherein the detectable label is selected from the group consisting of radioisotopes, fluorescent compounds, colloidal metals, chemiluminescent compounds, bioluminescent compounds, enzymes, substrates, cofactors and inhibitors.

26. The composition of matter according to any one of claims 1-25 further comprising a physiologically acceptable excipient.

27. A population or subpopulation of cells, wherein substantially all of the cells express or are isolated, concentrated or enumerated on the basis of expression of at least one of BDCA-1, BDCA-2 and BDCA-3.

28. The composition according to claim 27, wherein at least 80% of the cells are BDCA-1$^+$.

29. The composition according to claim 27, wherein at least 90% of the cells are BDCA-1$^+$.

30. The composition according to claim 27, wherein at least 95% of the cells are BDCA-1$^+$.

31. The composition according to claim 27, wherein at least 80% of the cells are BDCA-2$^+$.

32. The composition according to claim 27, wherein at least 90% of the cells are BDCA-2$^+$.

33. The composition according to claim 27, wherein at least 95% of the cells are BDCA-2$^+$.

34. The composition according to claim 27, wherein at least 80% of the cells are BDCA-3$^+$.

35. The composition according to claim 27 where at least 90% of the cells are BDCA-3$^+$.

36. The composition according to claim 27 wherein at least 95% of the cells are BDCA-3$^+$.

37. A population or subpopulation of dendritic cells, wherein substantially all of the cells express or are isolated, concentrated or enumerated on the basis of expression of BDCA-4.

38. The composition according to claim 37, wherein at least 80% of the cells are BDCA-4$^+$.

39. The composition according to claim 37 where at least 90% of the cells are BDCA-4$^+$.

40. The composition according to claim 37 wherein at least 95% of the cells are BDCA-4$^+$.

41. The dendritic cells of any of claims 12-14, and 29-40 wherein the cells are substantially activated.

42. A composition comprising the cells of any one of claims 12-14 and 28-41 and a physiologically acceptable excipient.

43. The composition according to claim 42, further comprising at least one antigen or antigenic peptide (T cell epitope).

44. The composition according to claim 43 wherein the antigen is loaded into the cells.

45. The composition according to claim 43 wherein the antigen is in solution with the cells.

46. The composition according to claim 43 wherein the antigen is presented on the cell surface.

47. The composition according to claim 43 wherein the cells have been treated to modulate cytosolic calcium concentration (at least transiently).

48. The composition according to claim 47 wherein the antigen is expressed by an exogenously derived gene or mRNA.

49. The cells according to claim 48 wherein the cells are pretreated with antigen-binding fragment specific for BDCA-2.

50. The composition according to claim 49 wherein the antigen is selected from the group consisting of a tumor cell antigen, a viral antigen, a bacterial antigen, a parasite-derived antigen, an autoantigen and/or an antigenic peptide (T cell epitope).

51. The composition according to claim 50 wherein the cell and antigen concentrations are effective to elicit an immune response in a subject upon administration to the composition of the subject.

52. The composition according to claim 51, wherein the immune response is directed against tumors, viruses, bacteria, parasites and fungi.

53. The composition according to claim 52, the antigen is a human tumor antigen and is selected from the group consisting of astrocytoma, fibrosarcoma, myxosarcoma, liposarcoma, oligodendroglioma, ependymoma, medulloblastoma, primitive neural ectodermal tumor (PNET), chondrosarcoma, osteogenic sarcoma, pancreatic ductal adenocarcinoma, small and large cell lung adenocarcinomas, chordoma, angiosarcoma, endotheliosarcoma, squamous cell carcinoma, bronchoalveolarcarcinoma, epithelial adenocarcinoma, and liver metastases thereof, lymphangiosarcoma, lymphangioendotheliosarcoma, hepatoma, cholangiocarcinoma, synovioma, mesothelioma, Ewing's tumor, rhabdomyosarcoma, colon carcinoma, basal cell carcinoma, sweat gland carcinoma, papillary carcinoma, sebaceous gland carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, bileduct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, testicular tumor, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma, leukemia, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease, breast tumors such as ductal and lobular adenocarcinoma, squamous and adenocarcinomas of the uterine cervix, uterine and ovarian epithelial carcinomas, prostatic adenocarcinomas, transitional squamous cell carcinoma of the bladder, B and T cell lymphomas

(nodular and diffuse) plasmacytoma, acute and chronic leukemias, malignant melanoma, soft tissue sarcomas and leiomyosarcomas.

54. The composition according to claim 49 wherein the antigen is a tolerogen.

55. The composition according to claim 54 wherein the tolerogen is specific to an autoimmune condition.

56. The composition according to claim 49 wherein the autoimmune condition is selected from the group consisting of rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Sjörgen's syndrome, lupus erythematosis, Good pasture's syndrome, Reiter's syndrome, scleroderma, vasculitis, polymyositis and dermatomyositis.

57. The composition according to claim 55 wherein the tolerogen is specific to organ transplantation.

58. The composition according to claim 56 wherein the organ transplantation is selected from the group consisting of heart, lung, liver, bone marrow, stem cell, kidney, skin.

59. A method for obtaining a composition comprising cells enriched for DCs comprising separating a mixture of human cells into a fraction wherein at least 80% of the cells in the fraction are BDCA-1^+.

60. The method according to claim 59, wherein at least 90% of the cells are BDCA-1^+.

61. The method according to claim 59, wherein at least 95% of the cells are BDCA-1^+.

62. A method for obtaining a composition comprising cells enriched for DCs comprising separating a mixture of human cells into a fraction wherein at least 80% of the cells in the fraction are BDCA-2^+.

63. The method according to claim 62, wherein at least 90% of the cells are BDCA-2^+.

64. The method according to claim 62, wherein at least 95% of the cells are BDCA-2^+.

65. A method for obtaining a composition comprising cells enriched for BDCs comprising separating a mixture of human cells into a fraction wherein at least 80% of the cells in the fraction are BDCA-3^+.

66. The method according to claim 65, wherein at least 90% of the cells are BDCA-3^+.

67. The method according to claim 65, wherein at least 95% of the cells are BDCA-3^+.

68. A method for obtaining a composition comprising cells enriched for DCs comprising separating a mixture of human cells into a fraction wherein at least 80% of the cells in the fraction are BDCA-4^+.

69. The method according to claim 68, wherein at least 90% of the cells are BDCA-4^+.

70. The method according to claim 68, wherein at least 95% of the cells are BDCA-4^+.

71. A method for isolating a substantially pure cell population comprising

a) obtaining a mixture of human cells;

b) substantially isolating cells from the mixture specifically recognized by an antigen-binding fragment specific for the antigen designated BDCA-2.

72. The method according to claim 71, wherein the antigen-binding fragment is or is derived from AC144, AD5-13A11, or AD5-4B8.

73. A method for isolating a substantially pure cell population comprising the steps of: a) obtaining a mixture of human cells; and b) substantially isolating cells from the mixture specifically recognized by an antigen-binding fragment specific for the antigen designated BDCA-3.

74. The method according to claim 73, wherein the antigen-binding fragment is or is derived from AD5-5E8 or AD5-14H12.

75. A method for isolating a substantially pure population of DCs comprising the steps of:

a) obtaining a mixture of human cells; and

b) substantially isolating cells from the mixture specifically recognized by an antigen-binding fragment specific for the antigen designated BDCA-4.

76. The method according to claim 75, wherein the antigen-binding fragment is or is derived from AD5-17F6.

77. The method according to any one of claims 63-76, wherein the source of cells is selected from the group consisting of fetal bone marrow, neonate bone marrow, adult bone marrow, fetal liver, peripheral blood and umbilical cord blood, leukopheresis, activated fresh blood, cultured cells, tonsil, spleen, lymph node, skin, airway epithelia, lung, liver, gut, Peyers patch and nasal.

78. The method according to claim 77 wherein the peripheral blood is mobilized.

79. The method according to claim 77 wherein the mobilization is by pretreatment with a composition selected from the group consisting of fLt3-Ligand and G-CSF.

80. The method according to claim 77 wherein the mobilization is by pretreatment with a composition selected from the group consisting of methods of inducing endogenous type I interferon IL-12 andIL-4.

81. A method for enumerating cells comprising the steps of: a) obtaining a mixture of cells; and b) labeling the cells with an antigen-binding fragment specific for any one or more of the antigens selected from the group consisting of BDCA-1, BDCA-2, BDCA-3, and BDCA-4.

82. The method according to claim 81 wherein the antigen is BDCA-1.

83. The method according to claim 81 wherein the antigen is BDCA-2.

84. The method according to claim 81 wherein the antigen is BDCA-3.

85. The method according to claim 81 wherein the antigen is BDCA-4.

86. A method of modulating immune capacity of DCs comprising the steps of: isolating a substantially pure population or subpopulation of DCs; and modulating the cytosolic calcium concentration (at least transiently) of the DCs.

87. The method according to claim 86, wherein modulation of DCs results in dendritic cells that preferentially induce a Th1 response to an antigen.

88. The method according to claim 87 wherein the antigen is an allergen, viral antigen, bacterial antigen, tumor antigen, parasite antigen and fungal antigen.

89. The method according to claim 86, wherein modulation of DCs results in dendritic cells that preferentially induce a Th2 response to an antigen.

90. The method according to claim 89 wherein the antigen is a selected from the group consisting of parasitic, autoantigen, bacterial and viral.

91. The method according to claim 86, wherein modulation of DCs results in dendritic cells that preferentially induce a Th3/Th-R response to an antigen.

92. The method according to claim 91 wherein the antigen is a selected from the group consisting of parasitic, autoantigen, bacterial, allergens and viral.

93. A method of screening for test agents for the presence of pharmaceutically effective agents comprising the steps of isolating or detecting, or enumerating a substantially pure population or subpopulation of cells with an antigen-binding fragment specific for any one or more of the antigens selected from the group consisting of BDCA-1, BDCA-2, BDCA-3, and BDCA-4; screening the cells with test agents; monitoring the response of the cells to the agents; comparing the response of the cells to the agents to cells exposed to a control agent; and determining whether the test agent modulated any one immunologic properties of the isolated, detected, enumerated cell.

94. The method according to claim 93, wherein the property of the cell is selected from the group consisting of antigen presentation, production of cytokines, response to cytokines, induction or suppression of a Th1 response, induction or suppression of a Th2 response, induction or suppression of a Th3/Th-R response ability to induce tolerance, induction of an antigen-specific response, induction of anergy in T cells, adjuvant activity and ability to mobilize intracellular calcium at least transiently.

95. A method to modulate an immunologic property of dendritic cell comprising altering cytosolic calcium concentrations (at least transiently) or altering the ability to mobilize intracellular calcium.

96. The method according to claim 95, wherein the modulation is selected from the group consisting of in vivo, in vitro and ex vivo.

97. The method according to claim 96 wherein modulation is by type I interferon.

98. The method according to claim 96 wherein modulation is by binding of an antigen binding fragment specific for an antigen selected from the group consisting of BDCA-1, BDCA-2, BDCA-3, and BDCA-4 or by inhibition of ligand binding to a BDCA.

99. The method according to claim 96 wherein modulation is by triggering BDCAs or inhibiting triggering thereof.

100. A method of treating a physiologic condition comprising administering to a subject in need thereof an effective amount of DC obtained by any one of claims 1-88.

101. The method according to claim 100, wherein the physiologic condition is a viral infection.

102. The method according to claim 101, wherein the viral infection is selected from the group consisting of hepatitis, HIV, influenza, rhinovirus, herpesvirus, lentiviruses, CMV and measles.

103. The method according to claim 100, wherein the physiologic condition is an autoimmune disease.

104. The method according to claim 103, wherein the autoimmune disease is selected from the group consisting of SLE, multiple sclerosis, arthritis, scleroderma and psoriasis.

105. The method according to claim 100, wherein the physiologic condition is an allergic response.

106. The method according to claim 105, wherein the allergic response is selected from the group consisting of allergies, hives and anaphylactic shock.

107. The method according to claim 106, wherein the allergic response is asthma.

108. The method according to claim 100, wherein the physiologic condition is cancer.

109. The method according to claim 108, wherein the cancer is selected from the group consisting of astrocytoma, fibrosarcoma, myxosarcoma, liposarcoma, oligodendroglioma, ependymoma, medulloblastoma, primitive neural ectodermal tumor (PNET), chondrosarcoma, osteogenic sarcoma, pancreatic ductal adenocarcinoma, small and large cell lung adenocarcinomas, chordoma, angiosarcoma, endotheliosarcoma, squamous cell carcinoma, bronchoalveolarcarcinoma, epithelial adenocarcinoma, and liver metastases thereof, lymphangiosarcoma, lymphangioendotheliosarcoma, hepatoma, cholangiocarcinoma, synovioma, mesothelioma, Ewing's tumor, rhabdomyosarcoma, colon carcinoma, basal cell carcinoma, sweat gland carcinoma, papillary carcinoma, sebaceous gland carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, bileduct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, testicular tumor, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, neuroblastoma, retinoblastoma, leukemia, multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease, breast tumors such as ductal and lobular adenocarcinoma, squamous and adenocarcinomas of the uterine cervix, uterine and ovarian epithelial carcinomas, prostatic adenocarcinomas, transitional squamous cell carcinoma of the bladder, B and T cell lymphomas (nodular and diffuse) plasmacytoma, acute and chronic leukemias, malignant melanoma, soft tissue sarcomas and leiomyosarcomas.

110. A method of modulating dendritic cell cytokine production comprising the steps of isolating a substantially pure population or subpopulation of dendritic cells with an antigen-binding fragment specific for any one or more of the antigens selected from the group consisting

of BDCA-1, BDCA-2, BDCA-3, and BDCA-4; and treating the cells with agents that modulate dendritic cell cytokine production.

111. A method of modulating in vivo dendritic cell cytokine production comprising administering to a subject in need thereof an effective amount of an agent that modulates dendritic cell cytokine production.

112. A method of generating a T cell and/or humoral immune response specific for an antigen comprising administering to a subject in need thereof an effective amount of a substantially pure population or subpopulation of dendritic cells loaded with the antigen and isolated with an antigen-binding fragment specific for any one or more of the antigens selected from the group consisting of BDCA-1, BDCA-2, BDCA-3, and BDCA-4 wherein the cells are modulated to induce a response selected from the group consisting of Th-1, Th-2 and Th-3/Th-R.

113. The method according to claim 112, wherein the antigen is loaded by transfection, loading with mRNA and cell fusion.

114. A method of generating a T cell or humoral immune response specific for an antigen comprising administering to a subject in need thereof an effective amount of a substantially pure population or subpopulation of dendritic cells loaded with the antigen and isolated with an antigen-binding fragment specific for any one or more of the antigens selected from the group consisting of BDCA-1, BDCA-2, BDCA-3, and BDCA-4 wherein the cells are modulated to induce a response selected from the group consisting of Th-1, Th-2 and Th-3/Th-R.

115. A polypeptide prepared by expressing in a recombinant host cell and purifying the expressed polypeptide away from total recombinant host cell components, wherein the polypeptide comprises about 5 contiguous amino acid residues from SEQ ID NO:2.

116. A composition comprising a purified polypeptide, wherein the polypeptide comprises about 5 contiguous amino acid residues from SEQ ID NO:2.

117. The composition of claim 116, wherein the polypeptide comprises a BDCA-2 extracellular domain.

118. A purified peptide consisting of 5 to 50 contiguous amino acid residues from SEQ ID NO:2.

119. A fusion protein comprising a polypeptide amino acid sequence linked to a polypeptide amino acid sequence that is not SEQ ID NO: 2, wherein the amino acid sequence comprises about 5 contiguous amino acid residues from SEQ ID NO:2.

120. The recombinant polypeptide of claim 119 comprising about 15 contiguous amino acid residues from SEQ ID NO:2.

121. The recombinant polypeptide of claim 120 comprising about 30 contiguous amino acid residues from SEQ ID NO:2.

122. The recombinant polypeptide of claim 120 comprising about 50 contiguous amino acid residues from SEQ ID NO:2.

123. The composition of claim 122, wherein the polypeptide comprises about 15 contiguous amino acid residues from SEQ ID NO:2.

124. The composition of claim 123, wherein the polypeptide comprises 30 contiguous amino acid residues from SEQ ID NO:2.

125. A polypeptide comprising at least one splice variant of BDCA-2.

126. The polypeptide according to claim 125 wherein the splice variant comprises exons 1-6.

127. The polypeptide according to claim 126 wherein the splice variant comprises exons 1, 3, 4, 5 and 6.

128. The polypeptide according to claim 126 wherein the splice variant comprises exons 1, 2, 4, 5 and 6.

129. The polypeptide according to claim 126 wherein the splice variant comprises exons 1, 2, 3, 5 and 6.

130. A polynucleotide or a complement thereof encoding BDCA-2 or a fragment thereof.

131. The polynucleotide according to claim 130 encoding at least 5 amino acid residues of SEQ ID NO: 2.

132. The polynucleotide according to claim 131 encoding at least 15 amino acid residues SEQ ID NO: 2.

133. The polynucleotide according to claim 131 encoding at least 30 amino acid residues SEQ ID NO: 2.

134. The polynucleotide according to claim 130 having SEQ ID NO: 1.

135. The polynucleotide according to claim 130 having at least 15 contiguous nucleotides of SEQ ID NO: 1.

136. The polynucleotide according to claim 130 having at least 75 contiguous nucleotides of SEQ ID NO: 1.

137. The polynucleotide according to claim 130 having at least 150 contiguous nucleotides of SEQ ID NO: 1.

138. A polynucleotide encoding at least one splice variant of BDCA-2.

139. The polynucleotide according to claim 138 wherein the splice variant comprises exons 1-6.

140. The polynucleotide according to claim 138 wherein the splice variant comprises exons 1, 3, 4, 5 and 6.

141. The polynucleotide according to claim 138 wherein the splice variant comprises exons 1, 2, 4, 5 and 6.

142. The composition according to claim 138 wherein the splice variant comprises exons 1, 2, 3, 5 and 6.

143. The polynucleotide of any one of claims 130-142 functionally attached to a promoter.

144. The polynucleotide of any one of claims 130-142 wherein the promoter is a recombinant promoter.

145. The polynucleotide of any one of claims 130-142 wherein the polynucleotide is a comprised in a recombinant vector.

146. A recombinant host cell comprising a polynucleotide of any one of claims 130-142.

147. The polynucleotide of any one of claims 130-142 or complement thereof wherein the region encoding SEQ ID NO: 2 or a fragment thereof hybridizes to the SEQ ID NO: 1 or the complement thereof under stringent hybridization conditions.

148. A method of inhibiting an interaction of a BDCA with a ligand specific therefor comprising contacting a composition comprising the BDCA and the ligand therefor with an effective amount of an agent that inhibits the interaction of BDCA-2, BDCA-3, or BDCA-4 with the ligand.

149. The method according to claim 148, wherein an interaction of a DC with a T cell is inhibited by contacting a composition comprising DC and T cells with an effective amount of an agent that inhibits the interaction of BDCA-2, BDCA-3, or BDCA-4 with the T cell.

150. The method according to claim 149 wherein the agent is an antigen-binding fragment specific for BDCA-2, BDCA-3, or BDCA-4.

151. The method according to claim 150 wherein the agent is administered in vivo or in vitro.

152. A method of treating inflammation comprising administering to a subject in need thereof an amount of an agent that inhibits the interaction of BDCA-2, BDCA-3, or BDCA-4 with the T cell effective to reduce inflammation in the subject.

153. A method of suppressing the expression of BDCA-2 in a cell comprising expressing a BDCA-2 antisense in the cell.

154. A transgenic animal comprising the polynucleotide of any one of claims 130-142.

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